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Justin Kopec
Syracuse University

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Abstract

Chromosome 22q11.2 Deletion Syndrome (22q11DS) is a genetic syndrome characterized by a variety of cognitive impairments, including difficulty with attention. Methodological confounds within the research investigating visual attention in individuals with 22q11DS make it difficult to understand temporal attention processing both in isolation and in a developmentally meaningful way. The current study addresses limitations of previous work by studying a specific temporal visual attention phenomenon, the attentional blink (AB), within a categorical rapid serial visual presentation task, and by utilizing developmentally appropriate sample matching procedures. Findings reveal that AB performance in individuals with 22q11DS is on par with two groups of typically developing control participants, one matched by chronological age and one matched by mental age. Individuals with 22q11DS performed similarly to both control groups on all measures of the AB, with the exception of reduced accuracy in reporting the first of two targets (T1 accuracy). These results suggest that aspects of temporal attention processing are intact in individuals with 22q11DS, and that attentional difficulties reported in previous research may be largely due to complexities in the spatial domain and/or difficulties sustaining attention in this population. Limitations and directions for future research are discussed.

Keywords: Chromosome 22q11.2 Deletion Syndrome, temporal attention, attentional blink, visual processing

Temporal Attention Processing in Individuals with Chromosome 22q11.2 Deletion Syndrome

by

Justin Kopec

B.A., University of Massachusetts Lowell, 2013

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Temporal Attention Processing in Individuals with Chromosome 22q11.2 Deletion Syndrome

Chromosome 22q11.2 Deletion Syndrome (22q11DS) is a genetic microdeletion syndrome that is characterized by a variety of physical anomalies along with behavioral and cognitive impairments (Antshel et al., 2007; Gothelf et al., 1999; Shprintzen et al., 1978; Stevens & Murphy, 2005), including intellectual disability (De Smedt, Devriendt, Fryns, Vogels, Gewillig & Swillen, 2007; Óskarsdóttir, Belfrage, Sandstedt, Viggedal & Uvebrant, 2005). Attention and concentration difficulties are specific areas of impairment that many individuals with 22q11DS experience (Simon & Luck, 2012). In fact, many of these individuals meet diagnostic criteria for disorders in which attention and concentration problems are paramount: 40% of children and adolescents with 22q11DS meet criteria for attention-deficit/hyperactivity disorder (AHDH; Antshel et al., 2006), while 20-30% meet criteria for schizophrenia in adulthood (Murphy, Jones & Owen, 1999; Pulver et al., 1994; Shprintzen, Goldberg, Golding-Kushner & Marion, 1992).

Experimental research suggests that attention processing in individuals with 22q11DS differs from that of typically developing individuals of the same age in several ways. For example, individuals with 22q11DS showed significantly slowed reaction times on invalidly cued trials of a spatial cueing task (Simon, Bearden, McGinn & Zackai, 2005) as well as on incongruent trials of a flanker task (Bish, Ferrante, McDonald-McGinn, Zackai & Simon, 2005; Sobin, Kiley-Brabeck, Daniels & Blundell, 2004). Individuals with 22q11DS also required significantly longer time intervals to implement inhibition of return (IOR) to a cued spatial location (Bish, Chiodo, Mattei & Simon, 2007) than typically developing peers of the same age. Across a variety of experimental paradigms, these results suggest that individuals with 22q11DS may experience difficulty with the disengagement of attention.

There are several limitations within the current literatures investigating attention processing in individuals with 22q11DS. One major limitation is that comparison groups have largely been matched to the 22q11DS sample by chronological age. This “deficit” model of comparison may be informative to an extent, but cannot differentiate whether observed differences are a result of general developmental delay or syndrome-specific impairments (Burack, Russo, Flores, Iarocci & Zigler, 2012). Given that intellectual impairments are common in this population, it would be informative to compare performance of those with 22q11DS to individuals who are at a similar developmental level in order to clarify this distinction. An additional limitation of previous research examining attention processing in this population is that many studies have utilized paradigms involving both spatial and temporal aspects of attention within the same task, making it difficult to tease out whether, and which, specific aspects of attention processing might be impaired.

The current study attempts to address these limitations by studying a specific visual attention phenomenon, the attentional blink, within a rapid serial visual presentation (RSVP) paradigm, which isolates the temporal domain of processing while keeping the spatial location of stimuli fixed. The current study also compares the performance of participants with 22q11DS to a group of typically developing individuals matched by mental age in addition to a group matched by chronological age which will help to clarify whether potential observed differences in attention processing can be explained by delays in development, or if they are more specifically impacted by the syndrome itself. These specifications allow for a more meaningful and precise understanding of the temporal attention processing capabilities of individuals with 22q11DS in the visual realm, which may also inform clinical practices concerning assessment

and intervention that would address precise differences in attention, should those be noted in relation to developmental expectations.

Chromosome 22q11.2 Deletion Syndrome

Chromosome 22q11.2 Deletion Syndrome (22q11DS) is a genetic syndrome caused primarily by de novo microdeletion of approximately 3 million base pairs of DNA encompassing 40 genes on the long (q) arm of chromosome 22 (Dunham, Shimizu, Roe & Chissoe, 1999; Morrow et al., 1995). Prior to the discovery that this specific deletion was responsible for a wide variety of phenotypic variations (de la Chapelle, Hervera, Koivisto & Aula, 1981; Kitsiou-Tzeli et al., 2004; Motzkin, Marion, Goldberg, Shprintzen & Saenger, 1993; Scambler et al. 1992), the syndrome was classified solely by specific physical and developmental features resulting in a variety of diagnostic labels including Velocardiofacial Syndrome, DiGeorge Syndrome, and conotruncal anomaly face syndrome, among others (Driscoll et al., 1993; Scambler et al., 1991). However, 22q11DS is a more inclusive label that encompasses all of these phenotypic variations, and is how the disorder will be referred to in the remainder of this document.

22q11DS is currently the second most common genetic syndrome, after Down syndrome, affecting approximately 1 in every 4000 to 6000 births (Botto et al., 2003; Driscoll et al., 1993; Gothelf & Lombroso, 2001). Although its phenotype can vary across individuals, the syndrome is often characterized by physical and developmental features such as cleft palate and throat problems, marked differences in facial appearance, heart defects, immunodeficiency, scoliosis, and low calcium levels (Gothelf et al., 1999; Shprintzen et al., 1978).

In addition to the physical challenges that accompany 22q11DS, the syndrome often manifests in a variety of behavioral problems, specific cognitive impairments, and psychopathology (Antshel et al., 2007; Stevens & Murphy, 2005). Prevalent behavioral and

cognitive issues demonstrated by individuals with 22q11DS include socioemotional difficulties, intellectual and learning disabilities, anxiety, and problems with attention and concentration (Golding-Kushner, Weller & Shprintzen, 1985; Swillen et al., 1997). Studies have reported that approximately 30-40% of study samples of individuals with 22q11DS were intellectually impaired (i.e., Full Scale IQ score < 70), with average IQ scores in the low 70s, and scores ranging from 50-109 (De Smedt et al., 2007; Óskarsdóttir et al., 2005). The psychological and cognitive phenotypes of the disorder also frequently result in individuals with 22q11DS obtaining psychiatric diagnoses in which attention problems are paramount, such as Attention-Deficit/Hyperactivity Disorder (ADHD), Generalized Anxiety Disorder (GAD), and schizophrenia, among others (Antshel et al., 2006; Antshel et al., 2007; Feinstein, Eliez, Blasey & Reiss, 2002; Green et al., 2009). Research has estimated that approximately 40% of children and adolescents with 22q11DS meet the diagnostic criteria for ADHD (Antshel et al., 2006), while 20-30% of adults with 22q11DS meet the diagnostic criteria for schizophrenia (Murphy, Jones & Owen, 1999; Pulver et al., 1994; Shprintzen, Goldberg, Golding-Kushner & Marion, 1992). In fact, 22q11DS is currently the strongest known molecular genetic risk factor for developing schizophrenia (McDonald-McGinn et al., 2016). Given that attentional impairments are reported in all of these conditions, further research to better understand the mechanisms of these processes in 22q11DS is merited.

Attention Processing in 22q11DS

Attentional impairment is often reported as a prevalent behavioral feature of 22q11DS, and these individuals often score higher than average on clinical measures that assess for difficulties with attention (Duijff, Klaassen, de Veye, Beemer, Sinnema & Vorstman, 2013; Furniss, Biswas, Gumber & Singh, 2011). However, there is limited empirical evidence

investigating the nature of these attentional difficulties in this population. A recent chapter on attentional impairment in children with 22q11DS cautions that attention is often so broadly defined that almost any performance deficit found in an experimental task could be called an attentional impairment (Simon & Luck, 2012). Therefore, results of experimental studies claiming attentional deficits in this population should be interpreted with caution. They define attention as “a process that selects some information and suppresses other information for the purpose of resolving competition” (Simon & Luck, 2012, p. 442). Depending on the source of competition, attention processing may interact with a variety of cognitive systems. For example, attention processing may interact with sensory processing when there are too many inputs to perceive at once, or with working memory encoding when there are too many percepts that need to be stored (Simon & Luck, 2012). Therefore, it is important to consider that certain aspects of attention processing may be intact in those with 22q11DS, while processes that rely on additional cognitive functions may be affected.

As an example, research has demonstrated that simple motor reaction time to a single stimulus is unimpaired in 7 to 14-year-old children with 22q11DS (with Full Scale IQ scores above 55) relative to typically developing (TD) children matched by chronological age (Simon, Takarae, DeBoer, McDonald-McGinn, Zackai & Ross, 2008). This suggests that, when competition is low, individuals with 22q11DS are able to attend to and respond to stimuli in a way that is similar to their TD peers. However, when engagement of attention is required, such as when individuals are required to select targets from an array of stimuli presented in varying spatial and temporal presentations, reaction time is often significantly slowed in those with 22q11DS compared to age-matched TD peers (Simon & Luck, 2012).

A study conducted by Simon, Bearden, McGinn & Zackai (2005) utilized an endogenous spatial cueing task in which triangular arrows were used to cue participants to attend to one side of a screen before stimuli were presented. Sometimes the cues were valid, and the target stimulus was indeed presented at the cued location. On other trials the cues were neutral and the triangular arrows pointed in both directions, providing no information about which side to attend to. Finally, some cues were invalid and the target stimulus was presented on the opposite side of the screen as the cue. Results showed that for valid trials, there were no significant differences in response times between individuals with 22q11DS and TD control participants of the same age. However, 22q11DS participants showed significantly slowed response times on neutral and invalid trials. In addition, participants with 22q11DS showed three times as many errors as comparison participants, primarily accounted for by errors on invalid trials. One possible interpretation of this is that 22q11DS participants were able to effectively “lock on” to the initially cued location which was beneficial on validly cued trials, but had more difficulty disengaging and re-orienting attention in order to locate and process targets when cues were neutral or invalid.

Bish, Chiodo, Mattei & Simon, (2007) used a different form of spatial cueing to examine whether attention was oriented toward objects or their location. In this task, four long rectangles were presented, one in each corner of a screen. Valid or invalid cues were presented before the target, which consisted of a shaded in portion of one of the rectangles. Valid cues bolded the outline of a portion of one of the rectangles at the exact location in which the target would appear. Invalid-within cues bolded the outline of a portion of one of the rectangles at a different location than the target would appear, but still within the same rectangle. Invalid-between cues bolded the outline of a portion of a different rectangle than the actual target would appear, but in

the correct spatial location of the rectangle (i.e. the target would appear in that location within a different rectangle on the screen). Figure 1 illustrates this paradigm as well as all variations of valid and invalid trial types. This study solely focused on reaction time of individuals, and unfortunately did not report accuracy rates for the two groups. Participants with 22q11DS between the ages of 7 and 14 years ($M = 9.08$, $SD = 2.37$) showed slowed reaction times in each of these three conditions (valid, invalid-between, and invalid-within) relative to age-matched TD comparison participants. Invalidity cost, which is the response time difference between validly cued trials and each type of the invalidly cued trials, revealed that participants with 22q11DS had a significantly higher invalidity cost in the invalid-between trials than typically developing participants, while there was no difference between the groups in invalid-within trials. This suggests that 22q11DS participants were relatively unimpaired in their ability to identify targets that appeared in the same rectangle as the invalid cue, but were significantly impaired when they were required to shift to a different rectangle than the cued rectangle to find the target. This further supports the idea that individuals with 22q11DS have trouble disengaging attention from an initially cued spatial location, but still relied on age-matched comparisons to draw conclusions.

A second experiment published by Bish et al. (2007) examined inhibition of return (IOR) in the same sample of children with 22q11DS between the ages of 7 to 14 years ($M = 9.08$, $SD = 2.37$). IOR is an orientation mechanism that, in typically developing individuals, leads to the enhancement or the facilitation of target detection at a cued location within 100-300ms after the cue, while impairing or inhibiting target detection at a cued location after 500-3000ms has passed (Klein, 2000). In this experiment, an initial cue (brightening of a square) on one side of the screen was presented first (50% valid), followed by a central cue (brightening of the central

fixation cross). The stimulus onset asynchrony (SOA) was short (100ms or 300ms) to facilitate target processing at the cued location, or long (500-700ms) to elicit IOR. Typically developing participants showed the expected pattern of results with significant facilitation when the central cue was presented for only 100ms, a trend towards facilitation when it was presented for 300ms, a trend towards IOR when it was presented for 500ms, and significant IOR when it was presented for 700ms. Conversely, participants with 22q11DS of the same age showed significant facilitation when the central cue was presented for 100ms, 300ms, and 500ms, and only showed significant IOR when it was presented for 700ms. These results suggest that IOR is somewhat intact in individuals with 22q11DS (i.e. significant inhibition was seen at 700ms for both groups), but that the facilitation of target detection may last for a longer period of time in this population than it does for age-matched TD peers. However, one limitation of the experiments conducted by Bish et al. (2007) is that they did not measure IQ or control for cognitive differences between groups.

Two additional studies have used the Attentional Network Task (ANT; Fan, McCandliss, Sommer & Posner, 2002) to examine attentional impairments in individuals with 22q11DS between the ages of 7 and 14 years ($M = 9.6$, $SD = 1.8$; Bish, Ferrante, McDonald-McGinn, Zackai & Simon, 2005) and between the ages of 5 and 11.5 years ($M = 7.6$, $SD = 1.6$; Sobin, Kiley-Brabeck, Daniels & Blundell, 2004). Neither study included measures of IQ. As part of the ANT battery, a flanker task was used in which participants were asked to determine the direction of the central arrow (left or right) when arrows on either side of the central arrow are congruent (pointing in the same direction) or incongruent (pointing in the opposite direction) with the central arrow. The flanker task makes up the executive network index (ENI) of this battery and was used as a measure of executive attention, which involves conflict resolution and control over

decision-making, error detection, and habitual response inhibition (Bish et al., 2005) The ENI is computed by subtracting response time on incongruent trials from response time on congruent trials. Both of the studies that used this task reported that individuals with 22q11DS showed significantly slower response times on both congruent and incongruent trials compared to the age-matched comparison group. In addition, individuals with 22q11DS showed a significantly larger executive network index compared to TD participants, indicating that they demonstrated a greater difference in response time on trials with high competition (i.e. incongruent) relative to response times on trials with low competition (i.e. congruent). In addition, Sobin et al. (2004) reported reduced accuracy in children with 22q11DS, which was accounted for by significantly lower accuracy rates on incongruent compared to congruent trials. Interestingly, accuracy rates did not differ depending on flanker type in the control group. These results suggest that individuals with 22q11DS may experience difficulty re-orienting attention to the central target when there are distractors competing for attentional engagement.

Although the above research has evidenced spatiotemporal attentional differences in individuals with 22q11DS compared to typically developing peers of the same age, the only study to our knowledge that has investigated temporal attention in isolation among individuals with 22q11DS, focused on temporal reproduction of sounds and perception of the length of audio and visual stimuli (Debbané, Glaser, Gex-Fabry & Eliez, 2005). Participants were first asked to tap their fingers to reproduce the tempo of tones they had just listened to. Results showed that individuals with 22q11DS between the age of 6 and 32 years ($M = 14.8$, $SD = 7.62$) significantly underestimated the inter-tone interval in their reproductions (their tapping was much faster than the original inter-tone interval) and they also showed greater overall variability in their reproductions compared to typically developing peers. In the second part of the experiment,

participants heard two sounds or saw two blue circles consecutively and were asked which of the two presentations were longer in duration. Results showed that individuals with 22q11DS had a significantly higher perceptive threshold than typically developing peers for both auditory and visual stimuli, indicating decreased temporal acuity.

In summary, individuals with 22q11DS showed no differences in reaction time compared to typically developing individuals of the same age on tasks with limited demands on the engagement of attention including simple reaction time tasks (Simon et al., 2008), valid trials of a spatial cueing task (Simon et al., 2005), and congruent trials of flanker tasks (Bish et al., 2005; Sobin et al., 2004). In contrast, when tasks became more difficult and required individuals to engage and disengage attention, individuals with 22q11DS showed significantly slowed reaction times compared to typically developing peers of the same age. This was true for invalidly cued trials of spatial cueing tasks (Bish et al., 2007; Simon et al., 2005) and incongruent trials of flanker tasks (Bish et al., 2005; Sobin et al., 2004). In an IOR task, 22q11DS participants showed significant facilitation of target detection for an increased period of time relative to TD peers, though there was no significant delay in their IOR (Bish et al., 2007). In addition, studies that reported accuracy results found decreased accuracy rates in individuals with 22q11DS relative to age-matched controls, which was primarily driven by significantly reduced accuracy on invalid or incongruent trials (Simon et al., 2005; Sobin et al., 2004).

Taken together, these studies seem to agree that, in the context of competing stimuli, individuals with 22q11DS may experience difficulty with the disengagement of attention. However, there are methodological limitations to previous research in this area that must be taken into consideration before making these specific claims. Specifically, many of the aforementioned studies that tested aspects of spatial attention, also included a temporal

component, since stimuli were presented in a sequence over the course of time. This is true for the spatial cueing tasks (Bish et al., 2007; Simon et al., 2005), as well as the IOR task (Bish et al., 2007). Thus, these studies make it difficult to rule out whether observed differences are related solely to spatial or temporal components, or some combination of the two. In addition, although the studies provide some useful information about attentional processing in individuals with 22q11DS, they all share a critical methodological oversight that may limit the interpretability of their results. This oversight is related to the matching procedures used by researchers, in which the performance of individuals with 22q11DS was exclusively compared to groups of TD individuals matched by chronological age, which is important because development delays in this group often lead to cognitive and intellectual functioning that is *not* equivalent to TD peers of the same age.

The current study aims to address these limitations by utilizing a task that isolates the temporal domain of processing while keeping the spatial location of all stimuli fixed in addition to comparing individuals with 22q11DS to TD participants at a similar developmental level. These are important steps to take in order to begin understanding attention processing in 22q11DS as differences that may be specific to the syndrome.

The Importance of Sample Matching Procedures

Sample matching procedures are particularly important when studying individuals with developmental and intellectual disability. Matching by chronological age (CA) can provide information about functional differences between atypically developing individuals and typically developing peers of the same age, which may be a direct result of atypical development. This has been referred to as the “deficit” model (Burack et al., 2012). CA matching may be useful in determining whether certain functions remain intact or are “spared” despite developmental

differences, given that the typically developing group has fully developed that particular area of functioning (Hodapp & Dykens, 2001). However, this method of matching cannot differentiate whether observed differences are resultant of a specific disorder or syndrome itself or consequent of general developmental delay that may be common across a variety of disorders. An alternative sample matching method is to match by mental age (MA). Matching by MA, which is traditionally calculated by multiplying CA by IQ and dividing by 100, can help to account for delays in cognitive development that may be present in atypically developing populations. MA essentially provides the age at which an individual's cognitive abilities would be considered average. For example, a 10-year-old with an IQ score of 50 would have the approximate mental age of a typical 5-year-old. MA matching is useful for discovering *relative* strengths or weaknesses of individuals with cognitive impairment compared to typically developing individuals who are at a similar developmental level (Burack et al., 2012; Hodapp & Dykens, 2001). The current study incorporates these matching procedures in order to gain a more comprehensive understanding of attentional processing in individuals with 22q11DS.

Although matching procedures are commonly used in the literature, some have cautioned against controlling for IQ in this way, particularly when studying individuals with neurodevelopmental disorders (Dennis, Francis, Cirino, Schachar, Barnes, & Fletcher, 2009). Dennis et al. (2009) argue that IQ scores are inherently linked to neurodevelopmental conditions through a complex interplay of individuals' genes, biology, cognition, education, and experiences, and cannot be separated out from the effects of specific conditions. They also argue that controlling for IQ can lead to overcorrected or anomalous findings about neurocognitive functioning of individuals with neurodevelopmental disorders. Keeping these cautions in mind, mental age matching was used in this study to get a better sense of the temporal attention

processing abilities of individuals with 22q11DS and the functional expectations of this group, which is often clouded by traditional chronological age matching.

The Attentional Blink

Rapid serial visual presentation (RSVP) is an experimental paradigm that isolates temporal attentional from spatial attention by presenting stimuli rapidly in a fixed spatial location. The ability of typically developing adults to detect rapidly presented target stimuli from a stream of distractor stimuli presented in the same spatial location has been well established using techniques such as RSVP (Forster, 1970; Potter, 1984). In a typical RSVP trial, target and distractor stimuli are presented rapidly in sequence at the same location on a display at rates of 10 items per second (Forster, 1970; Potter, 1984). Participants are told which target(s) to watch for in the stream, and are asked to report them at the end of each trial. In these paradigms, stimuli can be symbols, digits, letters, words, or pictures and targets often differ from distractor stimuli by feature (e.g. color) or by category (e.g. letters or numbers).

When a second target is presented in the RSVP stream within a specific time frame following the first target, it is often completely missed. This phenomenon has been termed the attentional blink, or AB (Broadbent & Broadbent, 1987; Raymond, Shapiro & Arnell, 1992). This metaphorical blink of attention refers to the evident impairment of individuals to identify the second of two targets presented in an RSVP trial, when its presentation falls within the range of 200-500ms after the first target (Broadbent & Broadbent, 1987; Raymond, Shapiro & Arnell, 1992). The AB has been observed across various types of target selection and is thought to be the result of either a limitation of visual processing speed or cognitive mechanisms that inhibit the rate of information processing (Dux & Marois, 2009; Martens & Wyble, 2010). Although the attentional blink is observed and measured in a very specific experimental context, the

phenomenon has real-world implications. For example, the AB may be relevant in a situation in which you are looking for your blonde-haired friend in a stream of people exiting a subway train. The first blonde-haired person you detect might deploy your attention and processing this person's face may cause you to completely miss your friend who exited the train directly after. This is just one example of how the AB may impact attentional processing in everyday life.

Since its discovery, several theories and models have attempted to explain the presence of the AB. One theory posits that resources used to process a single target need to be freed before a second target can be encoded into memory. This resource depletion theory, originally referred to as the two-stage model, is derived from evidence that making the first target easier to process through a variety of manipulations (e.g. making targets and distractors more easily discriminable) results in the second target being processed more frequently, reducing the depth of the AB (Chun & Potter, 1995). In this model, Stage 1 involves rapid detection of targets based on known features or categories (such as color or letter). Essentially all stimuli in the RSVP are assumed to be processed at this stage. Once a potential target is detected in Stage 1, Stage 2 is initiated which involves full identification and consolidation of the target for later report. This theory posits that this second stage is capacity limited and likely exceeds the duration of a given stimulus within an RSVP, resulting in subsequent stimuli, including targets, being “missed” during the AB period (Chun & Potter, 1995; Dux & Marois, 2009; Potter, Chun, Banks & Muckenhoupt, 1998; Raymond, Shapiro & Arnell, 1992).

In contrast to this resource depletion theory, another theory proposes that the AB may function as a useful adaptation of the visual system in which attention is momentarily diverted in order to better encode important information (Wyble, Bowman & Nieuwenstein, 2009; Lagroix, Spalek, Wyble, Jannati & Di Lollo, 2012). This theory, referred to as episodic segmentation,

suggests that the visual system may segment information into discrete chunks that can be more easily stored in memory in the correct temporal order. This idea stems from evidence that the onset of the AB begins after a delay of approximately 200ms, and if the second target is shown directly after the first (referred to as lag-1) prior to the typical AB onset, it is often easily seen and correctly reported (Raymond, Shapiro & Arnell, 1992; Chun & Potter, 1995). This is referred to as lag-1 sparing, because the second target is “spared” from the AB and is thought to be processed and encoded with the first target as a single episode. As further evidence of this theory, when lag-1 sparing occurs and both targets are accurately reported, they are often reported in reverse order (Chun & Potter, 1995), indicating that individuals may be processing them simultaneously. These instances are referred to as “swaps,” and although they are not exclusive to lag-1 presentations of the second target, they are significantly more likely to occur when the two targets are in close temporal proximity to one another (Chun & Potter, 1995). Recent research on the AB in children has found that younger children experience diminished accuracy in target reporting (Dye & Bavelier, 2010; Heim, Benasich, Wirth & Keil, 2015; Heim, Wirth & Keil, 2011; Russo, LeBlanc, Shea, Kates & Wyble, 2016), a significantly shallower, or less prominent AB (Russo et al., 2016), slower recovery rate from the AB (Dye & Bavelier, 2010; Garrad-Cole, Shapiro & Thierry, 2011) little to no lag-1 sparing (Heim et al., 2015; Heim et al., 2011), and significantly more swaps (Russo et al., 2016) when compared to older children and to an even greater extent when compared to adults. These findings corroborate the theory of the AB as a developmental adaptation that strengthens over the course of typical development.

The Attentional Blink in Clinical Populations Related to 22q11DS

Although the AB phenomenon has been well established and studied extensively in typically developing adults, far fewer studies have examined its occurrence in clinical

populations. To our knowledge, the AB has never before been studied in individuals with 22q11DS. There are, however, some existing studies that have investigated this phenomenon in individuals with schizophrenia and ADHD, which may be informative given overlapping attentional impairments and the high incidence of these disorders in individuals with 22q11DS.

There are currently six existing studies that have investigated the attentional blink in schizophrenia (Cheung, Chen, Chen, Woo & Yee, 2002; Li, Lin, Yang, Huang, Chen & Chen, 2002; Mathis, Wynn, Breitmeyer, Nuechterlein & Green, 2011; Mathis, Wynn, Jahshan, Hellemann, Darque & Green, 2012; Wynn, Breitmeyer, Nuechterlein & Green, 2006). All of these studies used categorical designs (participants had to identify target letters in a stream of distractor numbers), and all but one (Su et al., 2015) reported that individuals with schizophrenia showed significantly poorer target detection accuracy compared to typically developing individuals matched by chronological age. All five studies reported an exaggerated or deeper attentional blink in those with schizophrenia and four of the studies (Cheung et al., 2002; Li et al., 2002; Mathis et al., 2011; Mathis et al., 2012) reported a protracted AB effect in schizophrenia patients compared to age-matched controls, indicating attentional impairment beyond the typical AB window of 200-500ms. The AB was reported to be exaggerated in schizophrenia patients compared to controls, even when controlling for overall poorer performance on a single-target RSVP task (Cheung et al., 2002; Mathis et al., 2011).

Similarly, studies investigating the attentional blink in individuals with ADHD have found that, compared to chronological age-matched typically developing participants, individuals with ADHD showed lower overall target accuracy (Armstrong & Munoz, 2002; Carr, Nigg & Henderson, 2006; Hollingsworth, McAuliffe & Knowlton, 2001; Li, Lin, Chang & Hung, 2004; Mason, Humphreys & Kent, 2005), a more exaggerated or deeper AB (Amandor-Campos,

Aznar-Casanova, Bezerra, Torro-Alves & Sánchez, 2016; Hollingsworth et al., 2001; Li et al., 2004; Mason et al., 2005), and a slower recovery from or longer-lasting AB (Armstrong & Munoz, 2002; Hollingsworth et al., 2001; Li et al., 2004). Most of these studies employed paradigms that require set-shifting in which the two to-be-reported items differ in their features (e.g. one target was a colored letter while another target or “probe” was a specified black letter). Set-shifting paradigms may be difficult to compare to paradigms in which both targets share the same features (as in the current study), as they may require additional or different attentional demands (Heim, Wirth, & Keil, 2011). However, these studies may still be informative in understanding general AB characteristics in individuals with attentional impairments.

The above studies reveal differences in the AB in individuals with schizophrenia and ADHD when compared to typically developing controls matched by chronological age. However, these studies may not capture differences specifically related to these disorders by failing to control for important confounding factors that may be present. One recent study investigating the AB in individuals with schizophrenia (Su et al., 2015) controlled for differences in temporal integration that are known to be present in individuals with schizophrenia. They achieved this by slowing down the stimulus presentation rate for those with schizophrenia compared to control participants, so that single-target accuracy was similar between the two groups. Matching individuals by specific ability, especially one that is relevant to the task at hand, is an alternative method of matching that is often used to account for developmental differences in clinical populations (Burack, Iarocci, Bowler & Mottron, 2002; Burack, Iarocci, Flanagan & Bowler, 2004). Su et al. (2015) found that, when controlling for temporal integration differences, individuals with schizophrenia performed similarly to typically developing individuals, suggesting no impairments in the AB. Another recent study (Donnadieu, Berger,

Lallier, Marendaz & Laurent, 2015) looked at the AB in 11-year-old individuals with ADHD compared to both an age-matched control group as well as a group of 8-year-old typically developing control participants. This 3-year age gap was meant to account for developmental delays in ADHD, since research has estimated that cortical development is delayed by approximately 3 years in children with ADHD (Shaw et al., 2007). Donnadieu et al. (2015) found that, although children with ADHD showed significantly lower overall target accuracy, slower recovery, and a protracted AB compared to CA-matched controls, their performance on these same measures was similar to children 3 years younger. Results of both the Su et al. (2015) and Donnadieu et al. (2015) studies suggest that AB differences in schizophrenia and ADHD may in fact be accounted for by developmental differences or delays, rather than impairments in temporal attention that are disorder-specific.

Investigating the AB in individuals with 22q11DS would provide insight into temporal attention processing in this population and allow for indirect comparisons to previous work investigating this mechanism in ADHD and schizophrenic patients. Isolating the temporal component of attention processing has not yet been done in this type of experimental paradigm within this population. Sample matching by both chronological as well as mental age will allow us to distinguish whether potential observed differences in temporal attention processing in this population are better explained by developmental differences or disorder-specific impairments. In the current study, we investigate the AB in individuals with 22q11DS, compared to typically developing individuals matched by both chronological age (CA) and mental age (MA).

Predictions of the Current Study

Because of the high incidence of ADHD and schizophrenia in adults with 22q11DS and the overlaps in attentional impairment, along with the lack of attentional blink research in this

population, many of the hypotheses of the current study were derived from the ADHD and schizophrenia AB literature. Drawing particularly from the studies that took developmental differences into consideration (Donnadieu et al., 2015; Su et al., 2015), we hypothesized that individuals with 22q11DS will show similar performance on measures of the attentional blink compared to MA matched typically developing control participants. Specifically, we expected to see no differences in terms of T1 accuracy (correct identification of the first target presented), T2|T1 target accuracy (correct identification of both targets presented), depth of the attentional blink, recovery from the attentional blink, or temporal order swaps. In contrast, we expected to see significant differences in all of these measures between individuals with 22q11DS and typically developing CA matched control participants. Specifically, we expected that individuals with 22q11DS would show reduced T1 and T2|T1 target accuracy, a shallower AB indicating lower developmental attainment, slower recovery from the AB, and significantly more swaps when compared to CA matched control participants. This pattern of results would indicate that, as shown in individuals with schizophrenic (Su et al., 2015) and ADHD (Donnadieu et al., 2015), impairments in temporal attentional functioning in 22q11DS are resultant of general developmental delay rather than disorder-specific impairments.

As an additional exploratory component of this study, we examined relationships between performance on the AB task and behavioral markers of ADHD and schizophrenia obtained from participants with 22q11DS. Specifically, attention problems and ADHD symptoms measured by the Achenbach System of Empirically Based Assessment, Adult Self-Report (ASEBA-ASR; Achenbach & Rescorla, 2003), as well as positive prodromal symptoms of schizophrenia measured by the Scale of Prodromal Symptoms (SOPS; Miller et al., 2003;

Miller et al., 1999), were compared to AB performance measures to explore potential relationships between these measures.

Method

Participants

Participants with 22q11DS were recruited through the Center for the Diagnosis, Treatment, and Study of VCFS at SUNY-Upstate Medical University from a larger sample of participants in a longitudinal psychosis risk factors study. This experiment was conducted during the fourth wave of data collection in the longitudinal study. All participants had a fluorescence in situ hybridization (FISH)-confirmed deletion in the q11.2 region of chromosome 22. Participants were excluded if they had any other identifiable neurological condition besides 22q11DS that may affect cognitive performance.

Typically developing children were recruited through word of mouth and through flyers placed in the community and delivered via school listservs. Typically developing adults were recruited through word of mouth and through the SONA research system, in which undergraduate students in Psychology participate in research to earn course credit. Participants were excluded if they reported non-corrected vision problems. Typically developing child participants were also excluded if their parents reported a history of academic or psychiatric problems.

Sixteen individuals with 22q11DS initially participated in the study. One participant's data was excluded due to poor performance, with accuracy on the task greater than 2 standard deviations below the mean, indicating that the participant either did not understand, or did not follow the directions. This resulted in a total of 15 22q11DS participants (7 female) with a mean chronological age of 20.74 years ($SD = 2.5$) included in the analyses. The Wechsler Adult

Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997) was used to measure the intelligence quotient (IQ) and subsequently calculate the mental age of each 22q11DS participant. The mean mental age of the 22q11DS group was 17.02 years ($SD = 3.5$). Mental age (MA) matched and chronological age (CA) matched typically developing control participants were selected from a larger group of participants who completed the same experimental task, based on closest match (i.e. minimal differences in MA or CA between individuals within the groups). All 22q11DS participants were successfully matched by mental age, resulting in 15 MA-matched typically developing control participants (12 female) with a mean chronological age of 17.06 years ($SD = 3.71$). The average difference between the MA of 22q11DS participants and the CA of matched TD participants was 5.34 months (max = 11.72 months, $SD = 3.49$ months). All 22q11DS participants were successfully matched by chronological age, resulting in 15 CA-matched typically developing control participants (9 female) with a mean chronological age of 20.86 years ($SD = 2.36$). The average difference between the CA of 22q11DS participants and the CA of matched TD participants was 2.89 months (max = 7.56 months, $SD = 2.52$ months). See Table 1 for participant characteristics and medication information.

Experimental Design

All participants completed a rapid serial visual presentation (RSVP) attentional blink task where they were required to identify targets that differed from distractors by category; i.e. targets were letters and distractors were numbers. In the task, two black letters (the targets) were embedded in a stream of black number distractors, and participants were asked to identify the two black letters at the end of each RSVP stream. Target stimuli included black uppercase letters A, B, C, D, F, H, J, and K, while distractor stimuli included black numbers 1, 2, 3, 4, 5, 6, 7, 8, and 9. Participants completed 234 trials of the task and were allowed to take short breaks

between blocks of trials if needed. Stimuli in the RSVP stream were presented at a rate of 1 item per 135ms with no inter-stimulus-interval. All stimuli were presented in 48 point Arial font in the center of the screen on a light grey background. Each trial consisted of 30 stimuli; 2 targets and 28 distractors. Trials began with a fixation cross in the center of the screen, presented for 200ms, followed by the RSVP stream, illustrated in Figure 2. The first target (T1) was presented anywhere between position 6 and 18 in the stream. The second target (T2) was presented anywhere between one and eight lags after T1. Lag indicates what position in the RSVP stream T2 is presented following T1 (i.e. lag 1 indicates that T2 is presented directly after T1 in stream, whereas lag 8 indicates that T2 is presented 8 positions after T1 with 7 distractors in between). This resulted in the following target onset asynchronies: Lag 1 (135ms), lag 2 (270ms), lag 3 (405ms), lag4 (540ms), lag 5 (675ms), lag 6 (810ms), lag 7 (945ms), and lag 8 (1080ms). As such, the lag 2 and lag 3 presentations of T2 would fall within the 200-500ms attentional blink period. T1 position and T1-T2 lag (which included a T1-only condition) were counterbalanced in a 13 by 9 design to ensure that these were evenly mixed.

Following each trial, two identical response screens were presented (one at a time) for the identification of T1 and T2. Each screen contained two rows of all possible targets, presented on a light grey background, along with the statements ‘I saw nothing’ and ‘I don’t know what I saw’ underneath. All participants were asked to verbally report which uppercase letter targets they saw in order, while the experimenter entered their responses on a standard keyboard.

All stimuli were presented using Matlab on either a Dell P2210 with a resolution of 1680 by 1000 pixels with a 60 Hz refresh rate or a Macintosh Mini with a screen resolution of 1680 by 1050 pixels with a 60 Hz refresh rate. Despite the slight difference in screen resolution, the visual angle of all stimuli were kept constant, subtending 1.2 degrees vertically and 1.3 degrees

horizontally from the center of the screen. The programs were initiated and programmed using Stream, a Matlab toolbox that uses Psychophysics toolbox (Brainard, 1997).

Clinical Measures

Participants with 22q11DS completed several clinical measures in addition to the experimental task. The Wechsler Adult Intelligence Scale–Third Edition (WISC-III; Wechsler, 1997) is a widely used measure of intelligence appropriate for use with individuals between the ages of 16 and 90 years. The WAIS-III has demonstrated good test-retest reliability ($r_s \geq .70$), excellent inter-rater reliability ($r_s \geq .90$), and good convergent validity with other common IQ tests such as the Stanford-Binet, Fourth Edition ($r = 0.88$; Wechsler, 1997).

The Achenbach System of Empirically Based Assessment, Adult Self-Report (ASEBA-ASR; Achenbach & Rescorla, 2003) is a self-reported assessment of behavioral, psychological, and adaptive functioning appropriate for use in adults between the ages of 18-59 years. Several empirically based scales including the Attention Problems subscale can be derived from responses on this measure, in addition to several scales based on diagnostic categories in the Diagnostic and Statistical Manual of Mental Disorders (DSM), including the Attention Deficit/Hyperactivity (AD/H) Problems subscale, which is meant to capture symptoms of ADHD. Both the Attention Problems and AD/H Problems subscales have demonstrated good test-retest reliability ($r_s \geq .84$), internal consistency ($\alpha_s \geq .84$), as well as reasonable convergent \ validity with related clinical measures ($r_s \geq .63$; Achenbach & Rescorla, 2003).

The Scale of Prodromal Symptoms (SOPS; Miller et al., 2003; Miller et al., 1999) is a 19-item scale designed to measure prodromal symptoms of schizophrenia and changes over time. The Positive Symptoms subscale contains five items and is the primary scale used for making a prodromal diagnosis of schizophrenia. The SOPS has demonstrated good predictive validity for

detecting prodromal symptoms that predict the development of schizophrenia, with high sensitivity (100% accurate) and specificity ($\geq 71\%$ accurate) at 6, 12, 18, and 24 months after administration (Miller et al., 2003). The scale has also demonstrated good inter-rater reliability with an intraclass correlation value of 0.75 for all four subscales combined (Miller et al., 2003).

Procedures

Informed consent was obtained from all participants 18 years and older, while parent or guardian consent and participant assent were obtained for individuals under the age of 18 years. All procedures were approved by the IRB of the respective institutions where data were collected. Participants with 22q11DS were administered the WAIS-III in order to obtain an IQ score and calculate mental age. To assess for behavioral markers of ADHD and schizophrenia, individuals with 22q11DS were assessed for prodromal symptoms of schizophrenia using the SOPS as well as attention problems and ADHD symptoms using the ASEBA-ASR. All participants then completed the AB task. Mean scores on all clinical measures can be found in Table 1. Following completion of the study, participants were compensated for their time and participation, either monetarily (\$10 per hour of participation) or with SONA course credit.

Results

Overview of Data Analyses

A series of statistical tests were carried out in order to evaluate the hypotheses of the current study. In all analyses, when the assumptions of sphericity were found to be violated by Mauchly's test of sphericity, corrected Greenhouse-Geisser estimates were used (notated as F_{GG}); otherwise sphericity was assumed (notated as F). To investigate differences in the accuracy of target reporting, T1 accuracy and T2|T1 accuracy were calculated for each participant at each lag. T2|T1 represents trials in which participants correctly identified both T2

and T1. In this study, T2 and T1 were considered correct even in instances when their temporal order was swapped (i.e. when T2 was reported as T1 and vice versa) to avoid confounding accuracy results with potential differences in ability to report targets in the correct temporal order, a method that has been used elsewhere (Russo, Kates, Shea, LeBlanc, & Wyble, 2016). Although both T1 accuracy and T2/T1 accuracy require attentional processing over time given that all targets are presented within a stream of stimuli over the course of several seconds, T2/T1 accuracy reflects the ability to maintain temporal attention processing after processing and encoding of the first target (T1), while T1 accuracy alone reflects the ability to encode the first target, but does not capture whether temporal attention is maintained in order to process subsequent targets in the stream. In this way, T2/T1 accuracy provides a measure of temporal attention processing, while T1 accuracy provides a baseline measure of single-target detection abilities.

Proportion of swaps was further investigated by calculating the number of trials in which each participant accurately reported T1 and T2 but in reverse order, compared to the total number of trials in which T1 and T2 were accurately reported, regardless of order. Separate repeated-measures (RM) ANOVAs were conducted for T1 accuracy, T2/T1 accuracy, and proportion of swaps, with the between-subjects factor of group (22q11DS, MA-matched controls, CA-matched controls) and the within-subjects factor of lag (8). Given the small sample size in this study, Bayesian RM ANOVAs were also conducted on all of these variables to provide stronger evidence of differences by group and lag.

Depth of the AB was measured by subtracting the mean accuracy at lags 2 and 3 (the AB period) from the mean at lags 7 and 8, similar to methods used in several other developmentally focused AB experiments (Colzato, Spapé, Pannebakker, & Hommel, 2007; Kelly & Dux, 2007;

Martens & Johnson, 2009; Russo et al., 2016). Similar to methods outlined elsewhere (Dye & Bavelier, 2010; Russo, Kates, & Wyble, 2017), rate of recovery from the AB was calculated for each participant in each task by determining the lag (between lags 3-8) at which T2/T1 accuracy reached 80% of maximum accuracy (based on highest accuracy score at lags 4-8). One-way ANOVAs and Bayesian one-way ANOVAs were conducted to evaluate differences between groups for both depth of the AB and rate of recovery from the AB.

Exploratory correlation matrices and Bayesian correlation matrices were used to examine the relationship between performance on the AB task and behavioral markers of schizophrenia and ADHD in individuals with 22q11DS. We used non-parametric Spearman correlations to correlate measures of AB task performance with raw scores on the Positive Symptoms subscale obtained from the SOPS, and Pearson correlations to correlate measures of AB performance with raw scores on the Attention Problems and Attention Deficit/Hyperactivity (AD/H) Problems subscales obtained from the ASEBA-ASR.

Major Analyses

T1 accuracy. For T1 accuracy (see Figure 3), a RM ANOVA revealed a main effect of group ($F(2, 42) = 9.14, p = .001, \eta^2 = .3$) in which the 22q11DS group ($M_{22q11DS} = .81, SE = .021$) showed significantly lower T1 accuracy than both MA matched controls ($M_{MA} = .90, SE = .021, p = .005$) and CA matched controls ($M_{CA} = .94, SE = .021, p < .001$), who performed similarly. There was also a main effect of lag ($F_{GG}(5.46, 229.13) = 3.42, p = .004, \eta^2 = .08$) in which overall T1 Accuracy at lag 1 ($M_{lag1} = .84, SE = .019$) was significantly lower than accuracy at all other lags ($ps < .04$) and accuracy at lag 2 ($M_{lag2} = .88, SE = .016$) was lower than accuracy at lag 7 ($M_{lag7} = .90, SE = .014, p = .04$), which had the highest overall accuracy across groups. There were no interactions between group and lag, suggesting that patterns of T1

accuracy were similar across groups despite overall lower accuracy in the 22q11DS group compared to the two control groups. The Bayesian RM ANOVA also showed strong evidence in favor of a model containing the main effects of lag and group ($BF_{10} = 604.97$) over all other models, similar to the frequentist statistics.

T2|T1 accuracy. For T2|T1 accuracy (see Figure 4), a RM ANOVA revealed a significant main effect of lag ($F_{GG}(3.1, 130.3) = 30.54, p < .001, \eta^2 = .42$) in which accuracy at lags 2, 3, and 4 were significantly lower than accuracy at all other lags ($ps < .001$), suggesting a typical AB pattern. T2|T1 accuracy at lag 5 was also lower than accuracy at lags 7 and 8 ($ps < .03$), indicating an overall recovery period from the AB. Neither a main effect of group nor an interaction between lag and group were observed, suggesting that there were no differences in the level or pattern of performance between groups in terms of T2|T1 accuracy. The Bayesian RM ANOVA also supported a model including the main effect of lag ($BF_{10} = 3.9 \times 10^{29}$) above all other possible models.

Proportion of swaps. For proportion of swaps (see Figure 5), a RM ANOVA revealed a main effect of lag ($F_{GG}(2.86, 120.19) = 38.4, p < .001, \eta^2 = .48$) in which a significantly higher proportion of swaps were made at lag 1 compared to all subsequent lags ($ps < .001$), as well as at lag 2 compared to all following lags ($ps \leq .02$). Neither a main effect of group nor an interaction between lag and group were observed, suggesting that there were no differences in the proportion or pattern of swaps between groups. The Bayesian RM ANOVA also supported a model including the main effect of lag ($BF_{10} = 2.7 \times 10^{35}$) above all other possible models.

Depth of the attentional blink. To measure the magnitude, or depth, of the AB (see Figure 6), a one-way ANOVA with depth of the AB (i.e., mean of lags 7 and 8 minus mean of lags 2 and 3 of T2|T1 accuracy) as the dependent variable and the factor of group revealed that

there were no significant differences in the depth of the AB between groups ($F(2, 42) = .031, p = .97$). The Bayesian one-way ANOVA also revealed support for the null ($BF_{10} = 1$) over a model including a main effect of group ($BF_{10} = 0.17$).

Rate of recovery from the attentional blink. To measure differences in rate of recovery from the AB, a one-way ANOVA with recovery lag (i.e., return to 80% accuracy of maximum accuracy) as the dependent variable and the factor of group revealed that there were no significant differences in the rate of recovery from the AB between groups ($F(2, 42) = .014, p = .99$). The Bayesian one-way ANOVA also revealed support for the null over a model including a main effect of group ($BF_{10} = 0.17$).

Relationships between attentional blink performance and symptomology. For the participants with 22q11DS, two-tailed Pearson correlations and Bayesian Pearson correlations were run between measures of the AB, including depth of the AB, rate of recovery from the AB, and mean T1 Accuracy, and raw scores on the ASEBA-ASR Attention Problems and AD/H Problems subscales (see Table 2). A significant correlation (see Figure 7) was found between Attention Problems raw scores on the ASEBA-ASR and rate of recovery from the AB ($r = .681, p = .005, BF_{10} = 11.19$). There was no significant relationship between Attention Problems and depth of the AB ($r = 0.443, p = .099, BF_{10} = 1.11$) or mean T1 Accuracy rates ($r = -0.309, p = .262, BF_{10} = 0.568$). A significant correlation (see Figure 8) was found between AD/H Problems raw scores on the ASEBA-ASR and rate of recovery from the attentional blink ($r = 0.638, p = .01, BF_{10} = 6.38$). There was no significant relationship between AD/H Problems and depth of the attentional blink ($r = 0.393, p = .15, BF_{10} = 0.836$), or mean T1 Accuracy rates ($r = -0.365, p = .18, BF_{10} = 0.724$). Due to a high rate of zero scores and otherwise very low overall symptom counts on the SOPS Positive Symptoms subscale for our sample, nonparametric Spearman

correlations and Bayesian correlations were conducted to examine relationships between depth of the AB, rate of recovery from the AB, mean T1 Accuracy, and positive symptoms of schizophrenia (see Table 3). No significant relationships were found between positive symptoms on the SOPS and depth of the AB ($r_s = 0.045$, $p = .81$, $BF_{10} = 0.33$), rate of recovery from the AB ($r_s = 0.076$, $p = .79$, $BF_{10} = 0.3$), or mean T1 Accuracy rates ($r_s = 0.058$, $p = .84$, $BF_{10} = 0.34$).

Discussion

Developments in the Understanding of Temporal Attention Processing in 22q11DS

The goal of the current study was to gain a clearer and more meaningful understanding of the temporal attention processing abilities of individuals with Chromosome 22q11.2 Deletion Syndrome from a developmental perspective. Previous research investigating attentional processes in 22q11DS suggests intact abilities on tasks that involve simple motor reaction time (Simon et al., 2008) or following valid spatial cues (Simon et al., 2005), but impaired abilities on more complex tasks that require inhibition of attention to invalid cues or distractors (Bish et al., 2007; Bish et al., 2005; Simon et al., 2005; Sobin et al., 2004). These experiments involve aspects of both spatial and temporal attentional processes, making it difficult to determine whether one or both of these domains are affected in individuals with 22q11DS. These studies also exclusively matched participants to typically developing individuals by chronological age, failing to account for differences in developmental level, which are important in understanding functional expectations.

Results of the current study, which isolated the temporal domain of attention processing by presenting all stimuli in a fixed spatial location, provide some clarification of previous findings and offer new and important pieces of information regarding attentional functioning in

22q11DS. First, results suggest that some elements of temporal attention processing are relatively intact in individuals with 22q11DS compared to both chronological and mental age-matched typically developing peers. Although the task was complex, involving several distractor stimuli presented over very short (135ms) intervals, individuals with 22q11DS were able to achieve similar rates of conditional T2 accuracy as both TD control groups. This suggests that attentional difficulties seen in previous studies were perhaps related to complexities in the spatial domain rather than temporal demands. This may help to clarify interpretations of previous findings, such that decreasing spatial complexities and spatial competition (e.g., by providing a valid cue to a spatial location where subsequent processing will need to take place), may facilitate temporal attention processing in these individuals, resulting in performance similar to TD peers. However, individuals with 22q11DS did exhibit lower rates of T1 Accuracy compared to both CA and MA matched control participants in the Category Task. Given similar levels of T2/T1 accuracy rates between groups, it could be the case that the approximate 10% difference in T1 accuracy reflects difficulty in sustaining attention in 22q11DS participants, such that they were able to attend to 10% fewer trials than controls, but on attended-to trials they were just as able to deploy attention and report both targets accurately. It is also important to note that the AB task employed in the current study only examined temporal processing in a specific context, in which targets and distractors differed by category, and it is possible that processing may differ in other contexts (e.g., feature-based tasks) in this population.

Results of the current study not only provide meaningful information about the temporal attention processing abilities of individuals with 22q11DS, but comparisons between the two TD groups in this experiment also provide insight into the typical developmental course of the AB, adding to the existing literature on this topic. Previous research has examined the AB in younger

children compared to older children and adults in an attempt to map AB changes over the course of development (Dye & Bavelier, 2010; Garrad-Cole, Shapiro, & Thierry, 2011; Heim, Benasich, Wirth, & Keil, 2015; Russo et al., 2016). While most existing studies have compared performance of younger and older children (age groups ranging from 7 to 15 years of age) to each other and to adults on various measures of the AB, our experiment contains a slightly older TD sample with a mean age of 17.06 years. Comparisons between this group and the older (adult) TD group in our experiment with a mean age of 20.86 years suggest that the AB is perhaps fully developed by the age of 17.

The use of appropriate sample matching procedures is particularly important when attempting to understand the functional abilities of individuals with disabilities from a developmental perspective (Burack et al., 2012; Hodapp & Dykens, 2001). Mental age matching is useful for discovering *relative* strengths or weaknesses of individuals with cognitive impairment compared to typically developing individuals who are at a similar developmental level. These comparisons are often more meaningful than comparisons to TD individuals of the same chronological age, as they provide more realistic and clinically relevant information about functional abilities given developmental attainment. In our sample, the CA and MA matched control groups were very close in age, with a mean age of 20.86 for the CA matched group, and mean age of 17.06 for the MA matched group. This was a result of the limited ranges in chronological age and developmental level of the 22q11DS participants in our particular sample. This was a limitation of the current study because it only allowed for examination of the AB in this relatively small range of participants with 22q11DS. As noted, results of this experiment suggest that many measures of the AB may be fully developed by the mean age of our MA matched group (and respectively the developmental level of our 22q11DS group). If the sample

had included younger children with 22q11DS, or individuals with more significant cognitive impairment, we would perhaps be able to examine more nuanced differences between groups, as previous research has confirmed that various measures of the AB change over the course of typical development (Dye & Bavelier, 2010; Garrad-Cole, Shapiro, & Thierry, 2011; Heim et al., 2015; Russo et al., 2016). This avenue for future research would allow us to determine if and where children with 22q11DS stray from a typical trajectory.

Comparisons to Comorbid Clinical Populations

Given the high rates of ADHD and schizophrenia in individuals with 22q11DS, as well as similar findings of attentional impairment across these conditions, indirect comparisons to existing AB research in ADHD and schizophrenia may be informative. Results of the current study are most consistent with Su et al. (2015) and Donnadieu et al. (2015), in that participants with 22q11DS performed similarly on measures of the AB compared to controls when accounting for developmental differences. In this experiment, the 22q11DS group also performed similarly to the CA matched group, which is inconsistent with most AB studies in schizophrenia (Cheung et al., 2002; Li et al., 2002; Mathis et al., 2011; Mathis et al., 2012; Wynn et al., 2006) and ADHD (Armstrong & Munoz, 2002; Carr, Nigg & Henderson, 2006; Hollingsworth, McAuliffe & Knowlton, 2001; Li et al., 2004; Mason, Humphreys & Kent, 2005), in which these participants exhibited worse performance compared to age-matched controls. This may be due in part to the slower stimulus presentation rate in our study (135ms) compared to the traditional 100ms rate used in the schizophrenia studies and ADHD studies. This additional time may have been enough to allow participants with 22q11DS to “catch up” to the TD adults in our study, who may be near ceiling at this speed. Another factor that may explain this difference, at least in comparison to the studies conducted with individuals with

ADHD, is that our 22q11DS participants were adults while the ADHD studies tested children. It is also possible that this finding is due to differences in the attentional processing capabilities of individuals with 22q11DS compared to individuals with schizophrenia or ADHD. Future research should consider directly comparing individuals with 22q11DS to individuals with schizophrenia and ADHD on AB tasks as well as other attentional tasks in order to gain a better understanding of overlaps and nuances in attentional processing abilities that may exist between these groups.

Within our 22q11DS sample, results revealed that higher raw scores on the Attention Problems subscale and the Attention Deficit/Hyperactivity (AD/H) Problems subscale of the ASEBA-ASR were related to a later recovery from the attentional blink period. This suggests that attention problems and ADHD symptoms reported on clinical measures may in fact be related to the temporal attention processes involved in the attentional blink task, and that more significant problems with related attentional mechanisms may impact performance on this task as well as performance and behavior in real-life situations. Interestingly, scores on both the Attention Problems and AD/H Problems subscales were largely in the typical range for our sample of individuals with 22q11DS (see Table 1), with few individuals showing clinically elevated levels of Attention Problems or ADHD symptoms. The ASEBA-ASR on its own is not considered a comprehensive or clinically meaningful assessment of ADHD. Therefore, these data only allow for speculation that there could be common attentional mechanisms impacted in 22q11DS and ADHD. Future research should examine nuances in AB performance between individuals with 22q11DS who do and do not meet diagnostic criteria for ADHD, as well as non-syndromal individuals with ADHD. A further limitation of the current study is that we were not able to obtain attention problems or ADHD symptom ratings for our TD participants. As such, it

is impossible to know whether similar relationships between AB performance and attention problems and ADHD symptoms exist in the TD population, or if this relationship is unique to 22q11DS.

While there were no significant relationships observed between positive prodromal symptoms of schizophrenia and measures of the AB, it is important to note that none of our participants had a diagnosis of, or met diagnostic criteria for schizophrenia. Few individuals in our sample exhibited prodromal symptoms as measured by the SOPS and only 1 of 15 obtained a score of 3 or above on any single item of the Positive Symptoms Subscale, which is considered the threshold for clinically significant, prodromal symptoms of psychosis. In addition, the mean age of our 22q11DS sample was younger than 21 years old, while schizophrenia is most typically diagnosed in the early to mid-twenties (Beiser, Erikson, Fleming, & Iacono, 1993; Manschreck, Maher, & Candela, 2004), suggesting, perhaps, that symptoms may not yet have fully manifested. Finally, the participants in this study were part of a much larger, longitudinal study of the development of 22q11DS. The task presented here was completed during the fourth wave of data collection, and several participants who had already converted to schizophrenia were too psychiatrically impaired to travel to our center to participate in this timepoint. Accordingly, the lack of relationship between the AB and measures of prodromal symptoms might be due to the restricted range of prodromal scores in the sample, rather than a lack of relationship between the AB and schizophrenia symptoms in this population.

Clinical Implications

Results of the current study yield important clinical considerations. Our findings suggest that the temporal attention processing abilities of individuals with 22q11DS are comparable to TD individuals matched by chronological age and developmental level, at least in some contexts.

This information may help to inform treatment and intervention strategies for individuals with 22q11DS who are experiencing attention problems. For example, knowing that attention difficulties may stem from spatial complexities and difficulty sustaining attention over long periods of time rather than from temporal demands, treatment may focus on improving spatial acuity, decreasing spatial disorganization in the living and learning environment, and providing short breaks during long tasks. These strategies may be particularly relevant for adolescents and adults with 22q11DS, who have reached a mental age of approximately 17 years or older. Further research should be conducted to determine whether these findings extend to younger children with 22q11DS.

Limitations and Future Directions

Limitations of the current study include a small sample size of individuals with 22q11DS with limited ranges in chronological age and cognitive ability. In addition, although we have attempted to relate the functional abilities of individuals with 22q11DS in the domain of temporal attention processing to what we know about these processes in schizophrenia and ADHD, no direct comparisons can be drawn since we have not examined non-syndromal individuals with schizophrenia or ADHD and our methods do not exactly match studies that have. Future research should examine temporal attention processing in 22q11DS in contextual variations of the attentional blink task (e.g., in a feature-based task) as well as in other experimental paradigms, and in younger children. Future work should also consider directly comparing performance of individuals with 22q11DS to individuals with schizophrenia and ADHD on AB tasks and other tasks that measure temporal attention processing to better understand the overlaps and nuances that may exist between these comorbid groups.

Table 1

Participant Characteristics and Scores on Clinical Measures

	22q11DS	CA match	MA match
CA	20.74 (2.5)	20.86 (2.36)	17.06 (3.71)
MA	17.02 (3.5)	-	-
WAIS-III Full Scale IQ Standard Score	81.7 (10.4)	-	-
ASEBA-ASR Attention Problems Raw score	7.13 (5.5)	-	-
ASEBA-ASR Attention Problems T score	56.2 (7.7)	-	-
SOPS Positive Symptoms raw score	1.53 (2.06)	-	-
N on medication	6 ^a	0	0

Notes. All statistics reported as Mean (Standard Deviation). CA = Chronological Age; MA = Mental Age; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; ASEBA-ASR = Achenbach System of Empirically Based Assessments – Adult Self Report; SOPS = Scale of Prodromal Symptoms.

^a Indicates the number of participants that were taking one or more medications (stimulants, benzodiazepines, anti-depressants or anti-anxiety) to manage symptoms associated with 22q11DS during their participation in the study.

Table 2

Exploratory Correlation Matrix between Measures of the Attentional Blink, Attention Problems, and ADHD Symptoms

	Depth of the AB	Recovery from the AB	Mean T1 Accuracy	ASEBA-ASR Attention Problems	ASEBA-ASR AD/H Problems
Depth of the AB					
Pearson's <i>r</i>	-	0.813***	-0.226	0.443	0.393
<i>p</i> -value	-	< .001	0.417	0.099	0.147
<i>BF</i> ₁₀	-	148.4	0.43	1.114	0.836
Recovery from the AB					
Pearson's <i>r</i>		-	-0.303	0.681**	0.638*
<i>p</i> -value		-	0.272	0.005	0.01
<i>BF</i> ₁₀		-	0.554	11.192	6.37
Mean T1 Accuracy					
Pearson's <i>r</i>			-	-0.309	-0.365
<i>p</i> -value			-	0.262	0.181
<i>BF</i> ₁₀			-	0.568	0.724
ASEBA-ASR Attention Problems					
Pearson's <i>r</i>				-	0.954***
<i>p</i> -value				-	< .001
<i>BF</i> ₁₀				-	2.63 X 10 ⁶
ASEBA-ASR AD/H Problems					
Pearson's <i>r</i>					-
<i>p</i> -value					-
<i>BF</i> ₁₀					-

Notes. * $p < .05$, ** $p < .01$, *** $p < .001$, AB = attentional blink, ASEBA-ASR = Achenbach System of Empirically Based Assessments – Adult Self Report, AD/H = Attention Deficit/Hyperactivity

Table 3

Exploratory Correlation Matrix between Measures of the Attentional Blink and Positive Prodromal Symptoms of Schizophrenia

	Depth of the AB	Recovery from the AB	Mean T1 Accuracy	SOPS Positive Prodromal Symptoms
Depth of the AB				
Spearman's r_s	-	0.851***	-0.304	0.045
p -value	-	< .001	0.271	0.875
BF_{10}	-	148.4	0.431	0.326
Recovery from the AB				
Spearman's r_s		-	-0.308	0.076
p -value		-	0.265	0.787
BF_{10}		-	0.554	0.320
Mean T1 Accuracy				
Spearman's r_s			-	0.058
p -value			-	0.837
BF_{10}			-	0.339
SOPS Positive Prodromal Symptoms				
Spearman's r_s				-
p -value				-
BF_{10}				-

Notes. *** $p < .001$, AB = attentional blink, SOPS = Scale of Prodromal Symptoms

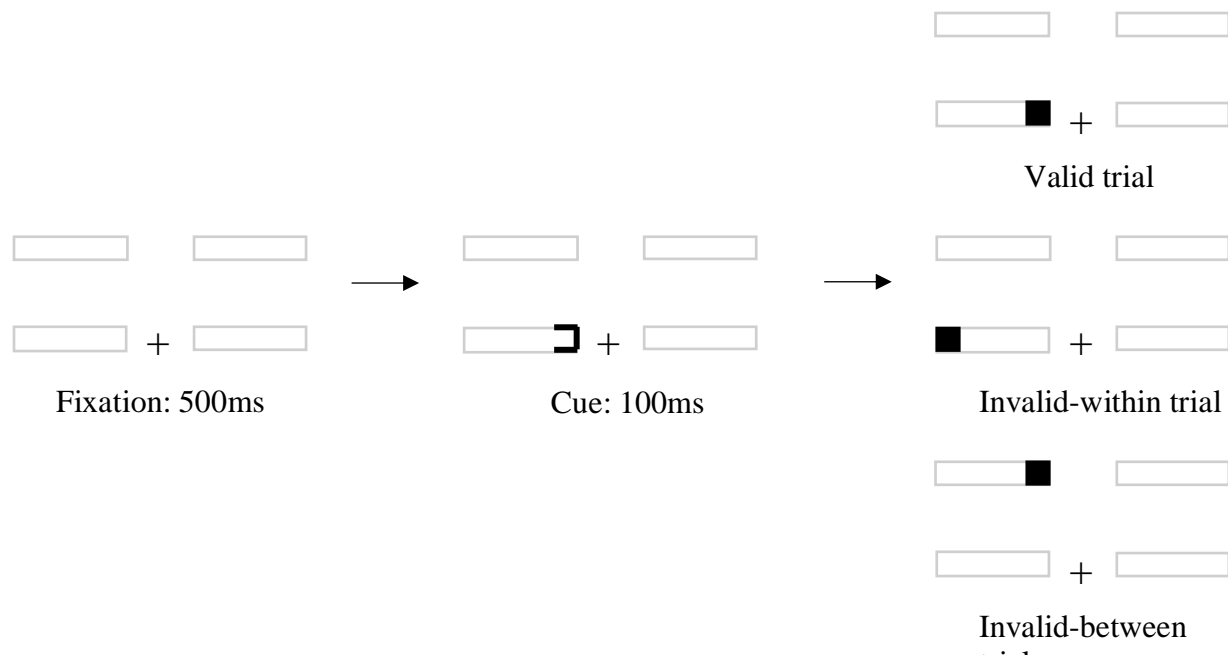


Figure 1. Demonstration of the spatial cueing task used in Bish et al. (2007). Each screen is presented over time from left to right from fixation, cue, and target presentation. Examples of valid, invalid-within, and invalid-between target presentation trials are shown on the right.

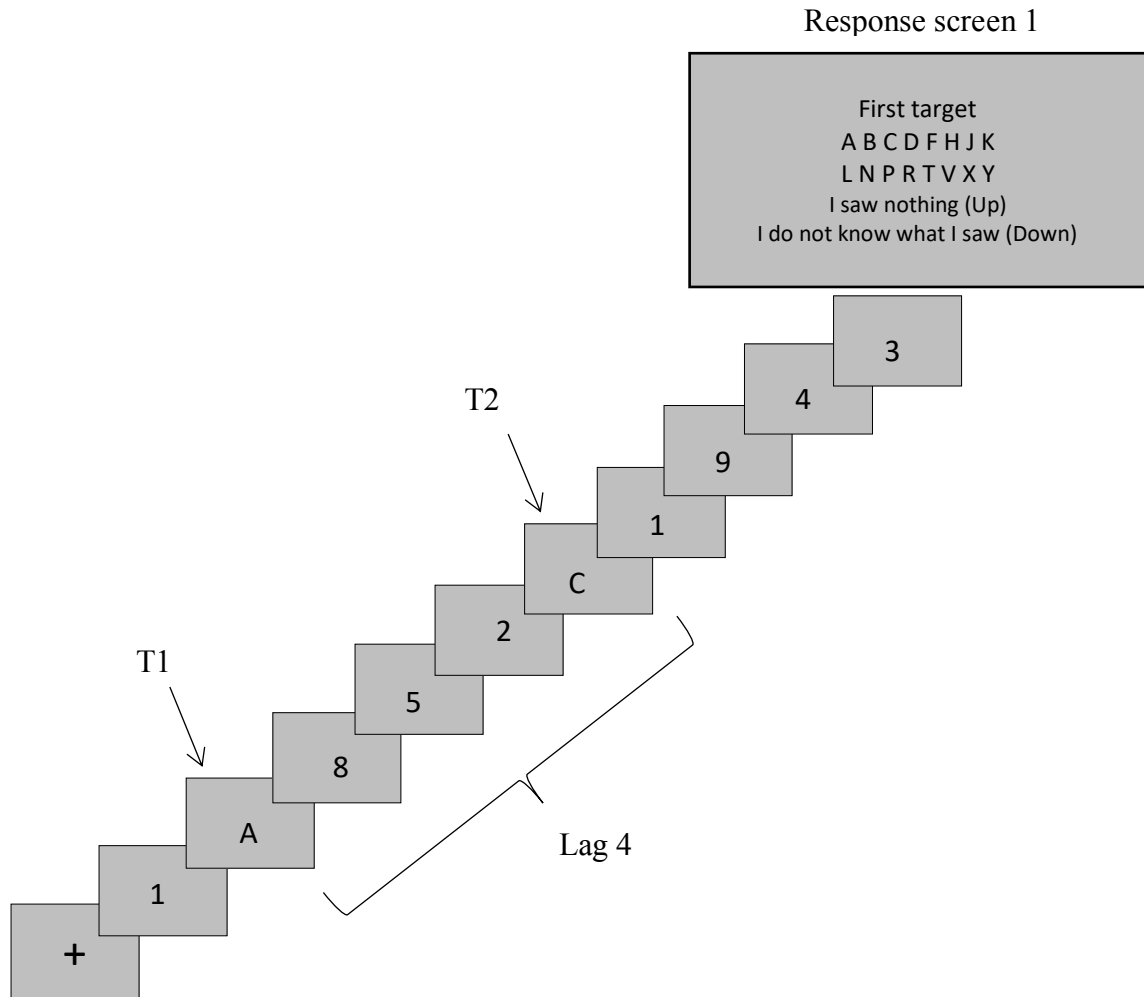


Figure 2. Attentional blink task: RSVP paradigm and response screen. This diagram depicts the fixation cross and individual letter (target) and number (distractor) stimuli presented in an RSVP trial. Targets and are shown below in lag 4 position. This diagram shows only 10 stimuli, while actual trials contained 30. The upper right had corner shows the response screen for T1, which was identical to the T2 response screen.

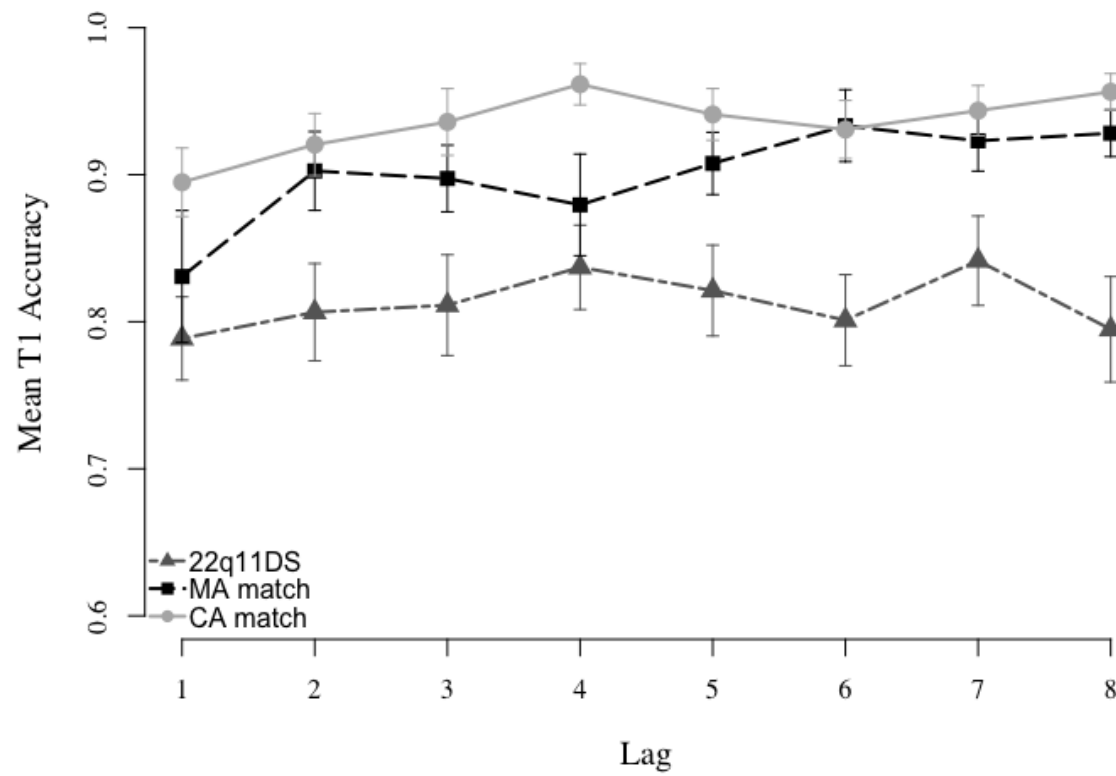


Figure 3. T1 accuracy. This figure shows accuracy rates by presentation lag of the first target (T1) for each of the three participant groups.

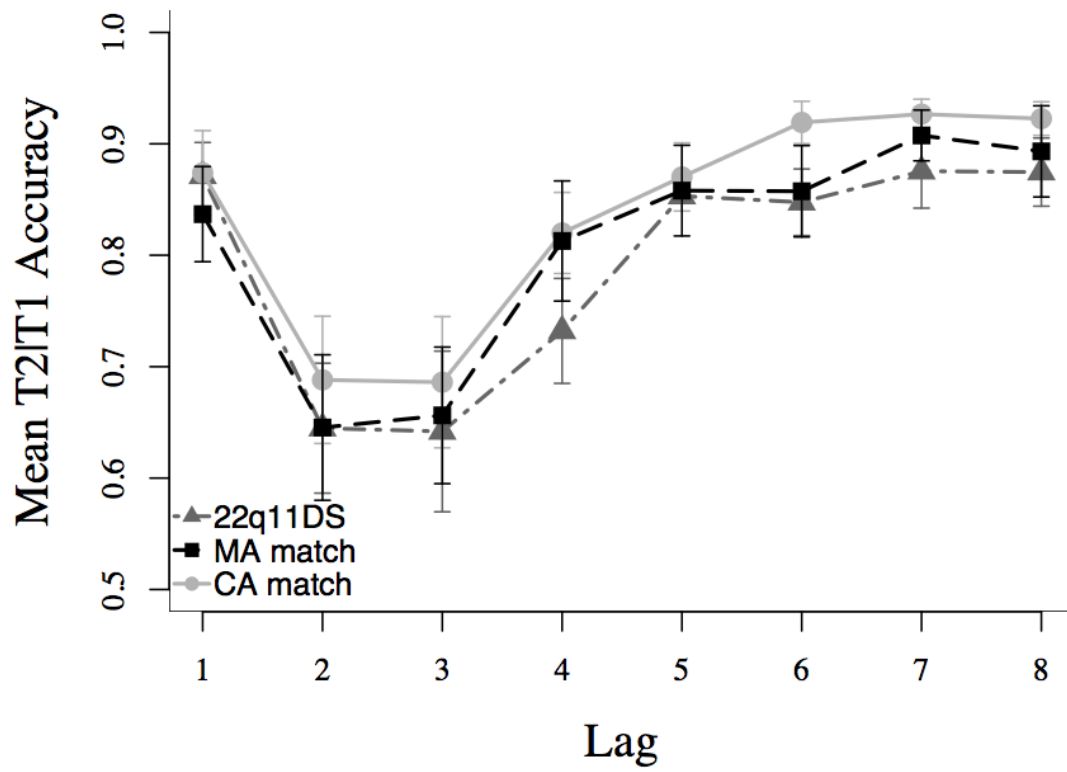


Figure 4. T2/T1 accuracy. This figure shows accuracy rates by presentation lag of the second target, given that the first target was also detected accurately (T2/T1), for each of the three participant groups.

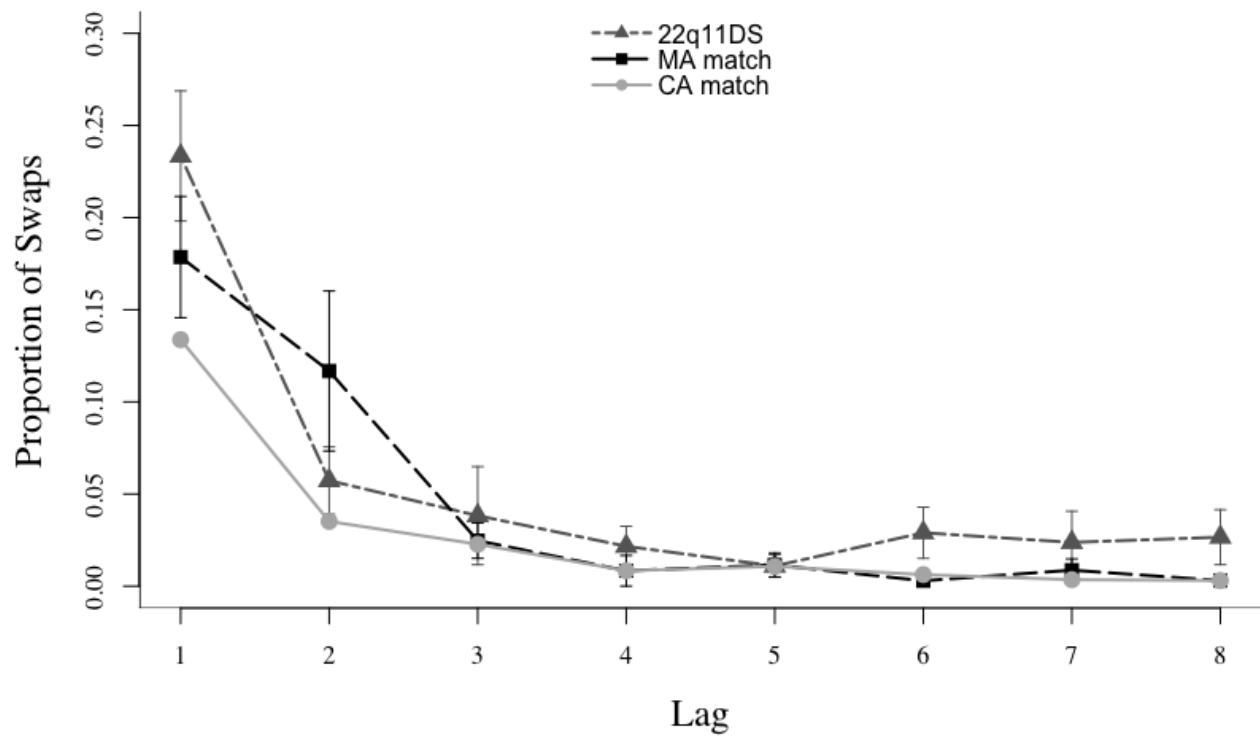


Figure 5. Proportion of swaps. This figure depicts the proportions of temporal order swaps of the two targets by presentation lag for each of the three participant groups.

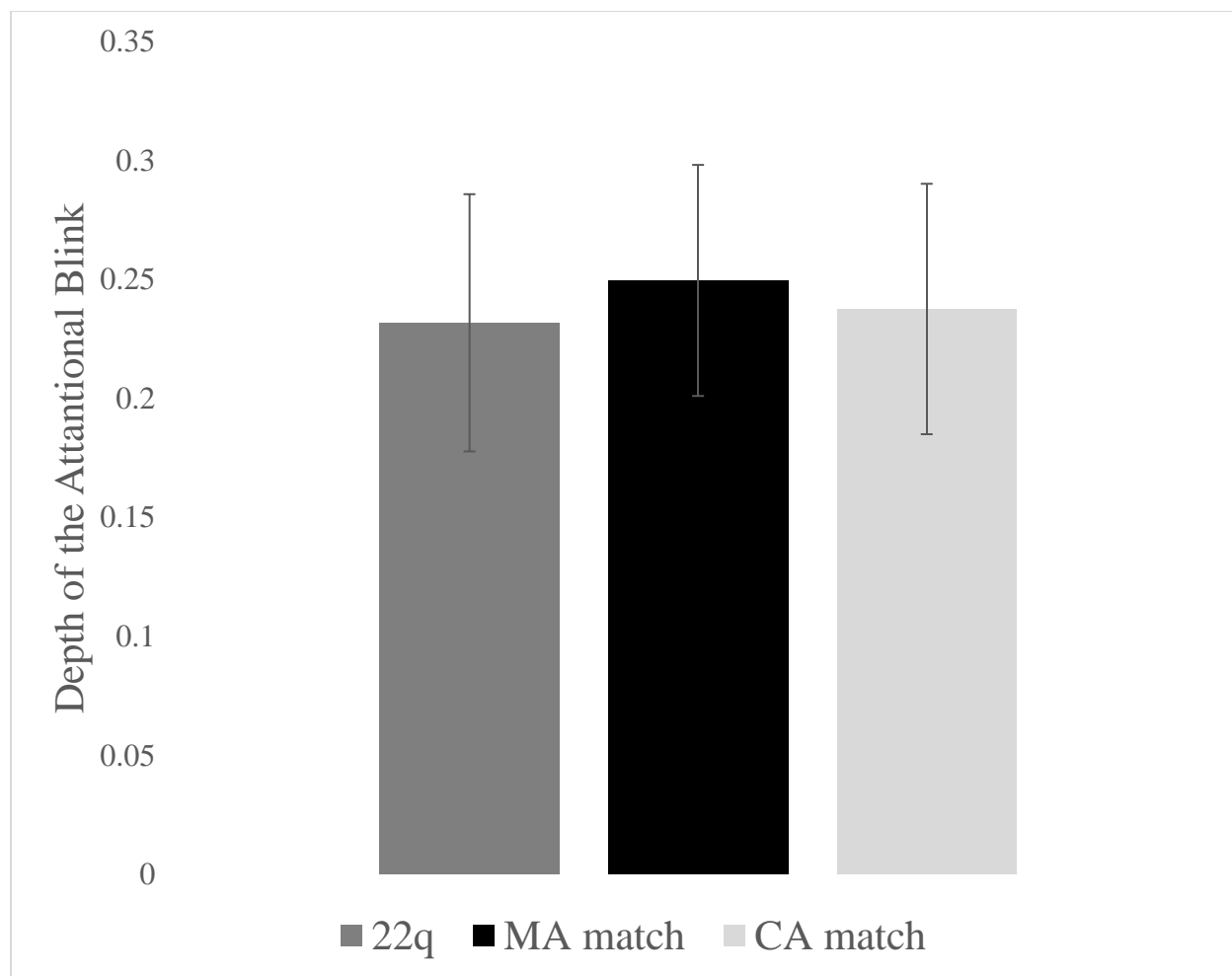


Figure 6. Depth of the attentional blink. This figure shows the average depth of the attentional blink for each of the three participant groups.

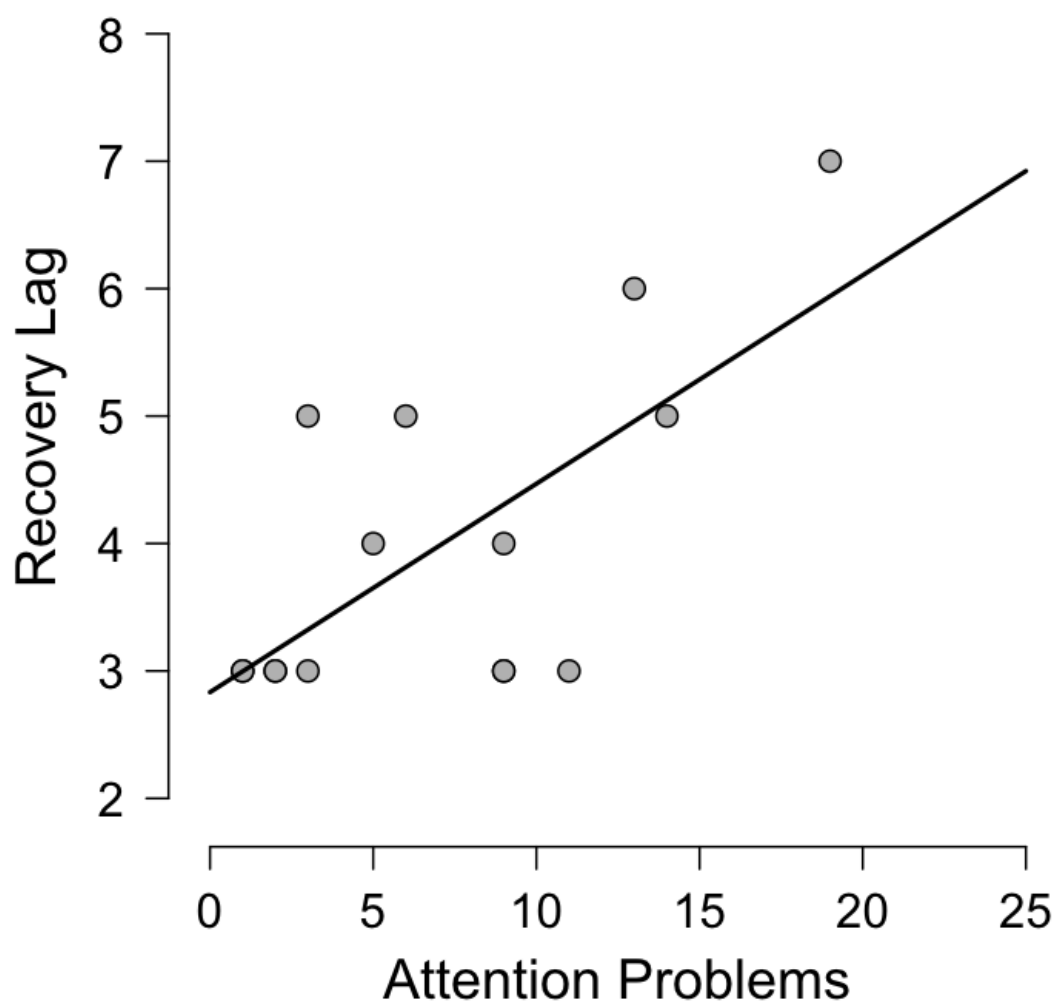


Figure 7. Correlation between attention problems and recovery from the attentional blink in 22q11DS. This figure shows a scatterplot of the correlation between the Attention Problems subscale scores on the ASEBA-ASR (x-axis) and rate of recovery from the attentional blink (y-axis) in participants with 22q11DS.

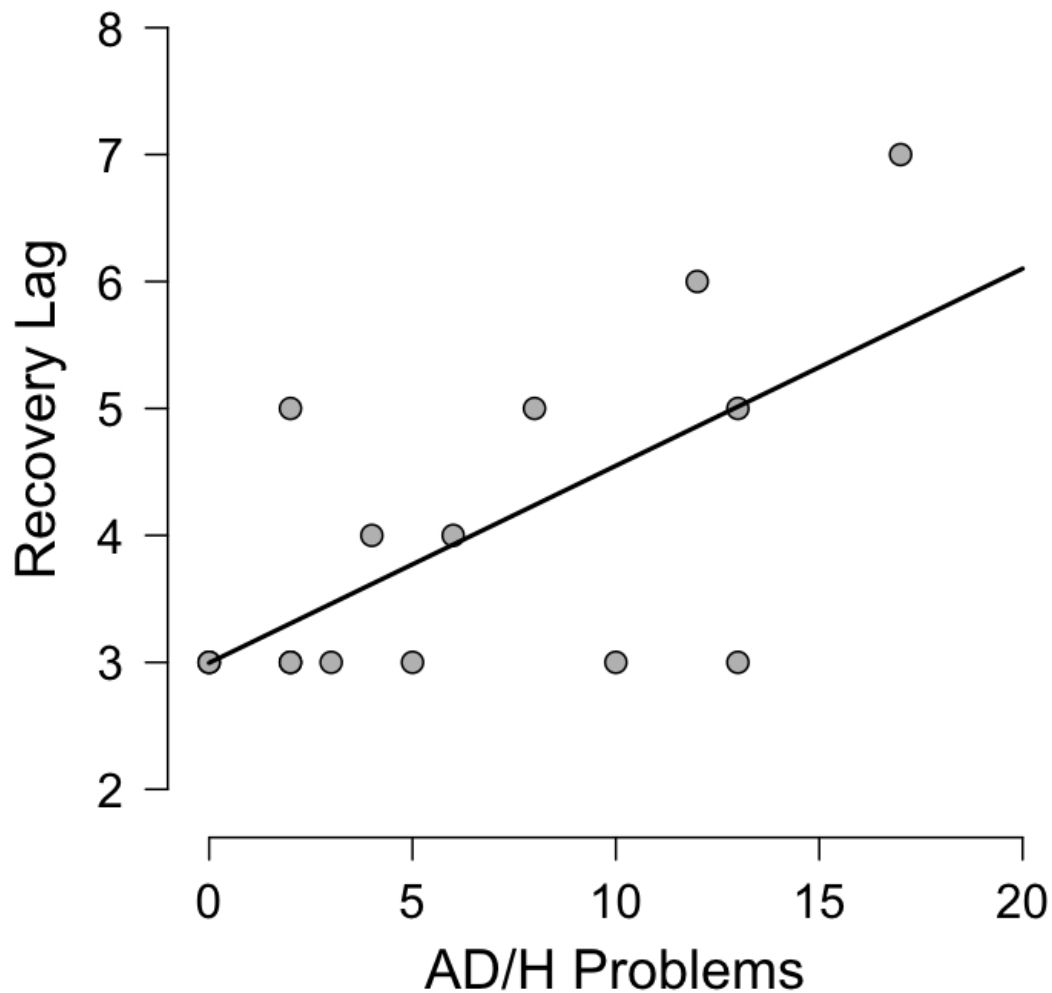


Figure 8. Correlation between Attention-Deficit/Hyperactivity (AD/H) symptoms and recovery from the attentional blink in 22q11DS. This figure shows a scatterplot of the correlation between the Attention-Deficit/Hyperactivity (AD/H) Problems subscale scores on the ASEBA-ASR (x-axis) and rate of recovery from the attentional blink (y-axis) in participants with 22q11DS.

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Justin Kopec**Vita****Contact:**

430 Huntington Hall
Syracuse University
Syracuse, NY 13244

Education:

Syracuse University

Department of Psychology, School Psychology Ph.D. program

2015 – present

University of Massachusetts Lowell

Department of Psychology, B.A.

2008 – 2013